Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: June 30, 2022

**Citation:** Alvarenga Martines LH, Gomides Marconato G, et al., 2022. The Effects of *Curcuma Longa* on the Osteoarthritis: A Systematic Review of Placebo-Controlled Clinical Studies, Medical Research Archives, [online] 10(6). https://doi.org/10.18103/mra.v10i6.2888



DOI
https://doi.org/10.18103/mra.v10i6.2888

ISSN: 2375-1924

REVIEW ARTICLE

# The Effects of *Curcuma Longa* on the Osteoarthritis: A Systematic Review of Placebo-Controlled Clinical Studies

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ABSTRACT

Osteoarthritis (OA) is a joint disorder characterized by chronic, degenerative, and irreversible inflammation leading to pain and disability. The standard drugs are ineffective for many patients and are usually associated with numerous side effects such as gastrointestinal complaints. *Curcuma longa* and its bioactive compounds have been considered for OA. The objective of this study was to perform a systematic review of the effects of *Curcuma longa* and its derivatives on OA. Pubmed, Cochrane, and Embase were searched, and PRISMA guidelines were followed to build this review. Only Randomized Clinical Trials (RCTs) that performed placebo-comparison were included. Most included studies showed that *Curcuma longa* or formulations prepared with curcuminoids can benefit the OA scores such as Visual Analog Scale, Knee injury and Osteoarthritis Outcome Score, Western Ontario and McMaster Universities Osteoarthritis Index; and Lequesne's pain functional index. The use of *Curcuma longa* extracts or curcuminoids can benefit patients with OA. Nevertheless, the available RCTs show treatment time, doses, and formulations heterogeneity. Thus, the standardization of RCTs can guide researchers and physicians on the dosages and formulations that are most effective in addressing this condition, which is very prevalent in the world's populations.

**Keywords:** *Curcuma longa;* curcuminoids; curcumin; arthritis; Osteoarthritis

## 1. INTRODUCTION

Osteoarthritis (OA) is a joint disorder characterized by chronic, degenerative, progressive, and irreversible inflammation. It can be caused naturally by aging (primary or idiopathic Osteoarthritis) or due to trauma, infections, or malformations that result in joint degeneration. Its symptoms are usually characterized by pain, functional weakness, and primary disability in more advanced stages. These conditions impose a substantial burden on individuals, the health system, and society since it is not effectively treatable [1-6].

In the early stages of degeneration, chondrocytes are stimulated in an attempt to repair tissue, with a consequent increase in the production of proteoglycans and collagen. Besides the migration of beneficial cells such as chondrocytes and chondroblasts there is also an increase in enzymes that degrade cartilage, such as disintegrins and metalloproteinases (collagenase and gelatinase). These enzymes are associated with the release of inflammatory cytokines such as Tumor Necrosis Factor-α (TNF-α), Interleukin 1-β (IL-1β), IL-6, and IL-17. The resulting loss of the cartilage leads to persistent friction followed by deformation of the bones related to the usual symptoms. Moreover, osteophyte formation, bone remodeling, and alterations in the synovium and joint capsule are observed. The degenerative process may affect any joints, but the knees, fingers, neck, lower back, and hips are most common [2,7-9]. Figure 1 shows the risk factors for developing the OA.

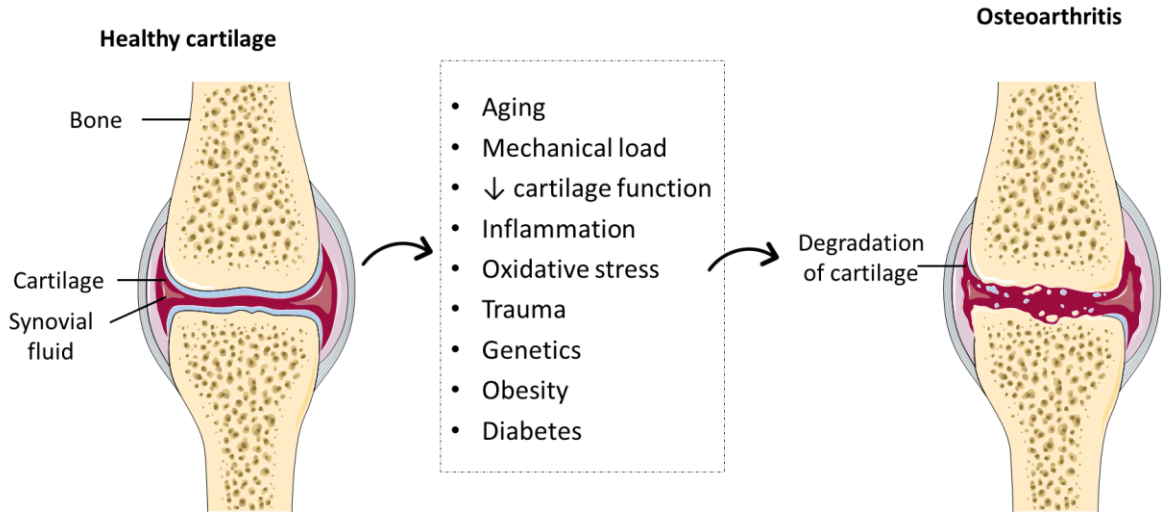


**Figure 1.** Risk factors related to the development of Osteoarthritis.

The available therapies for OA remain a challenge. The traditional therapeutic approach uses analgesics, corticosteroids, and nonsteroidal anti-inflammatory drugs. However, in addition to the costs, the use of these drugs is associated with numerous side effects such as gastrointestinal conditions, tiredness, hyperglycemia, problems with immunity, swelling, agitation, and insomnia, mainly if they are prescribed for long periods. Long-term use of these drugs leads to renal and cardiovascular adverse events [10-12]. There is a need for new therapeutic approaches that help treat OA for these reasons. Therefore, studies have shown that plants with anti-inflammatory potential can improve patients' symptoms and may reduce the use of medications that promote many adverse effects [13-15].

Curcuma longa and derivatives are the most studied for the treatment of OA. The main bioactive compounds of this plant are curcuminoids. The major are curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Several studies have shown that curcumin exhibits remarkable antioxidant and anti-inflammatory actions due to inhibiting pro-inflammatory pathways such as cyclooxygenase-2 (COX-2), prostaglandins, leukotrienes, and the release of pro-inflammatory biomarkers such as TNF-α, IL-1β, IL 6, and IL-8. By inhibiting the signaling pathways mediated by Nuclear Factor Kappa β (NFkβ) and Inhibitor of nuclear factor kappa-B kinase subunit beta (IKK), there is a reduction in the processes associated with pain and other symptoms reported by patients with OA. In this sense, Curcuma longa can benefit the patient with OA since it is related to reducing the inflammatory process that is characteristic in these patients[31].

For these reasons, the objective of this study is to perform a systematic review of the effects of *Curcuma longa* and curcuminoids on OA.

## 2- LITERATURE SEARCH

### 2.1 Focused question

The focused question used for this review was: Which are the effects of *Curcuma longa* on Osteoarthritis?

### 2.2 Language

Only studies in English were selected.

### 2.3 Databases

For this study, we searched the PubMed, EMBASE, and COCHRANE databases. The descriptors used were *Curcuma longa* or curcumin and Osteoarthritis. These mesh terms helped identify trials that reported using *Curcuma longa* or turmeric or curcumin or curcuminoids and knee osteoarthritis. The PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines were followed to perform this review [16] (Figure 1).

### 2.4 Study selection

In this study, we included trials that reported the effects of *Curcuma longa* or its derivatives in the therapeutic approach of OA. The inclusion criteria were Double-blind, Randomized Clinical Trials (RCTs), and placebo-controlled studies. We only included studies that were full texts. Only studies that used a placebo were included.

The exclusion criteria included in vitro studies, animal studies, clinical trials associated with different herb formulations, reviews, studies not in English, poster presentations, case reports, and editorials. Reviews were consulted to help in the discussion section but were not included in the systematization of the data.

### 2.5 Data extraction

The selected period for the search was January 2012 to May 2021. The included studies are shown in Table 1.

### 2.6 Quality Assessment

The possible risk of bias (regarding the selection of the study, detection, and reporting biases of each clinical trial) was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions to perform this quality assessment [17].

## 3- RESULTS OF THE LITERATURE SEARCH

According to the inclusion and exclusion criteria (Figure 2), we selected fourteen RCT that are found in Table 1 [18-31]. The studies were performed mainly in India (six studies) and other countries around the world: Thailand (two studies), Iran (two studies), Belgium (one study), Japan (one study), Italy (one study), Armenia (one study), Spain (one study), and Tasmania-Australia (one study). All these RCTs used *Curcuma longa* or its extracts or formulations orally in 1,167 patients (about 70% were women).

Most studies evaluated OA scores such as VAS (Visual Analog Scale), KOOS (Knee injury and Osteoarthritis Outcome Score), WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), LPFI (Lequesne's pain functional index), and PGADA (Patient Global Assessment of Disease Activity). These studies showed that the use of *Curcuma longa* extracts and formulations with curcuminoids can improve the above-mentioned scores and can reduce biomarkers of inflammation such as IL-4, IL-6, TNF-α, C reactive protein, and oxidative markers such as malonaldehyde. The reduction of oxidative stress and inflammation contributes to the improvement of OA scores.

Except for Rahimina et al [23], who did not find differences between the placebo and the treated group for C Reactive Protein, IL-4, IL-6, and Prostaglandin E2, all the included trials indicated that the *Curcuma longa* could bring benefits for the patient with OA. As already mentioned, *Curcuma longa* reduces pain and improves physical function and stiffness (at different scores such as VAS, KOOS, LPFI, WOMAC, and PGADA).

The trials that compared the plant with ibuprofen[28,69] or diclofenac [18,25,32] showed that *Curcuma longa* exhibits similar effects compared to these drugs, without the side effects regularly reported by patients that are treated with these drugs.

The most common adverse events observed in the trials were nausea, dyspepsia, and diarrhea, but *Curcuma longa* extracts or formulations are considered well-tolerated and safe.

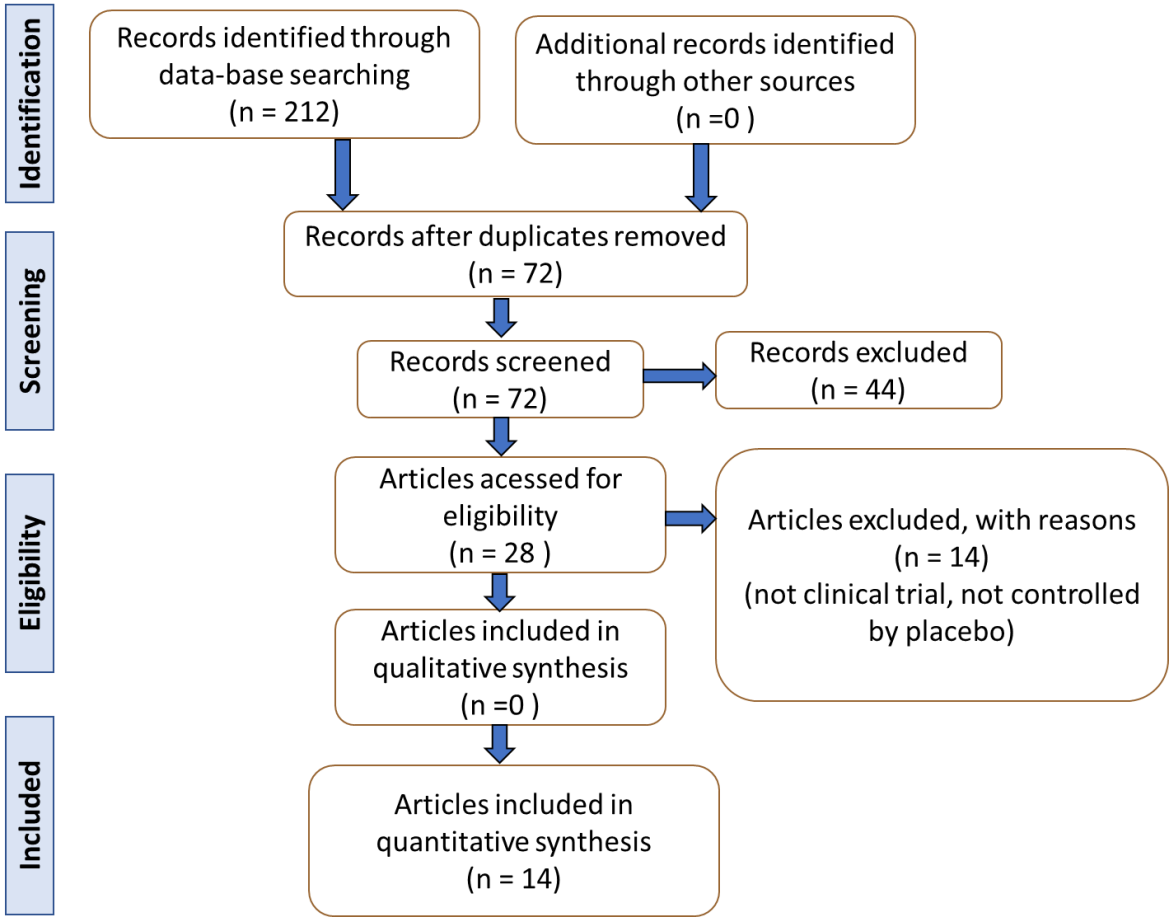


**Figure 2.** Flow diagram showing the study selection (PRISMA guidelines).

## 4. SOME ASPECTS OF *CURCUMA LONGA*

*Curcuma longa*, also named turmeric, is a perennial rhizomatous plant belonging to the Zingiberaceae family. *Curcuma* is one of the largest genera in this family. It is found in tropical and subtropical regions from South China to India, Papua New Guinea, northern Australia, and South America [33]. It has been considered to treat several illnesses since ancient times in India and China. It can be cosidered antibacterial, antioxidant, anti-inflammatory, antidiabetic, anticarcinogenic, antiobesity, and hepatoprotective agent, besides being used as a spice, food flavors, and cosmetics [34-38].

The compounds present in *Curcuma longa* are mainly flavonoids, terpenoids, anthocyanin, tannins, and organic acids. Curcuminoids are among the main bioactive components. Curcumin accounts for almost 77% of the total; bisdemethoxycurcumin represents about 17), and demethoxycurcumin is around 3%. They are nontoxic polyphenolic compounds that can exhibit immunosuppressant actions [39,40]. They can downregulate the expression of cyclooxygenase-2, lipoxygenase-5, inducible nitric oxide synthase, and several other pro-inflammatory mediators, such as TNF-α, IL-1β, IL-6, and IL-8. Moreover, curcuminoids can inhibit the phosphorylation and elimination of the Nuclear Factor of Kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). They may activate the γ receptor mechanism started by the peroxisome proliferator, decreasing the inflammation scenario stimulated by NFκB pathways. The antioxidant effects are associated with the upregulation of antioxidant enzymes such as superoxide dismutase and catalase [41-43]. Figure 3 summarizes some results of *Curcuma longa* and its curcuminoids.

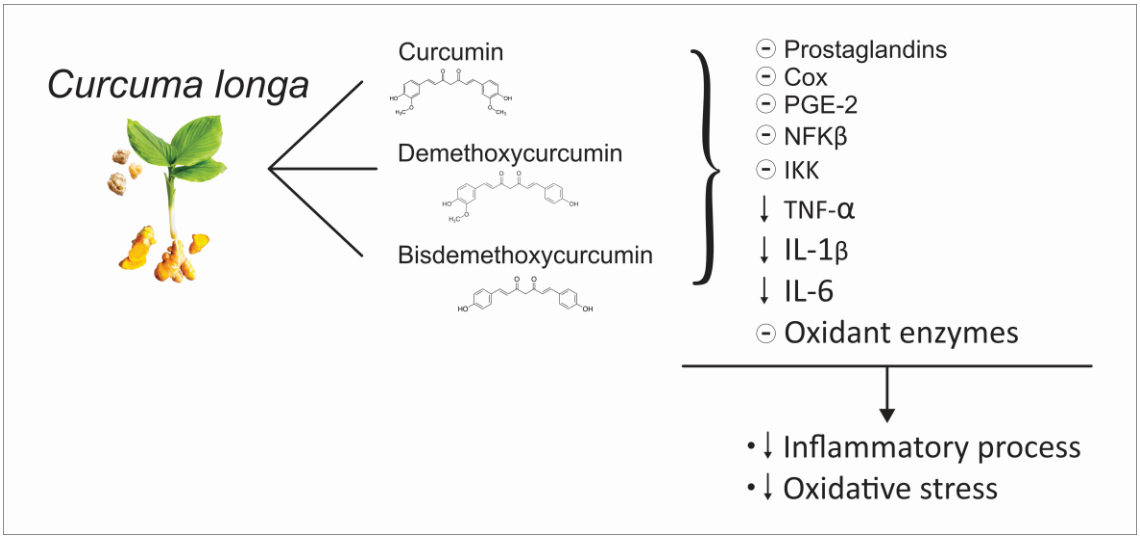


**Figure 3.** The anti-inflammatory and antioxidants of *Curcuma longa* and its bioactive compounds. COX: cyclooxygenase-2; IKK: I Kappa Beta Kinase; IL: Interleukin; NFκβ: Nuclear Factor kappa beta; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; TNF-α: Tumor Necrosis Factor-alpha.

*Curcuma longa* and curcumin have shown that they are safe for human consumption, mainly if they are administrated by oral delivery. They are considered non-mutagenic, non-genotoxic, and generally recognized as safe (GRAS). Clinical investigations have shown that the oral safe dose is 6 g daily for 4–7weeks. Nevertheless, minor adverse effects an occur (dyspepsia, nausea, diarrhea) [38,44,45]

## 5. PHYSIOPATHOLOGY OF OSTEOARTHRITIS: AN OVERVIEW OF THE GENERAL ASPECTS

The pathophysiology of Osteoarthritis is complex, not fully understood, and involves numerous inflammatory and oxidative events that we would not be able to explore here fully. Below are just a few points from these events.

Below are just a few points from these events (Figure 4).

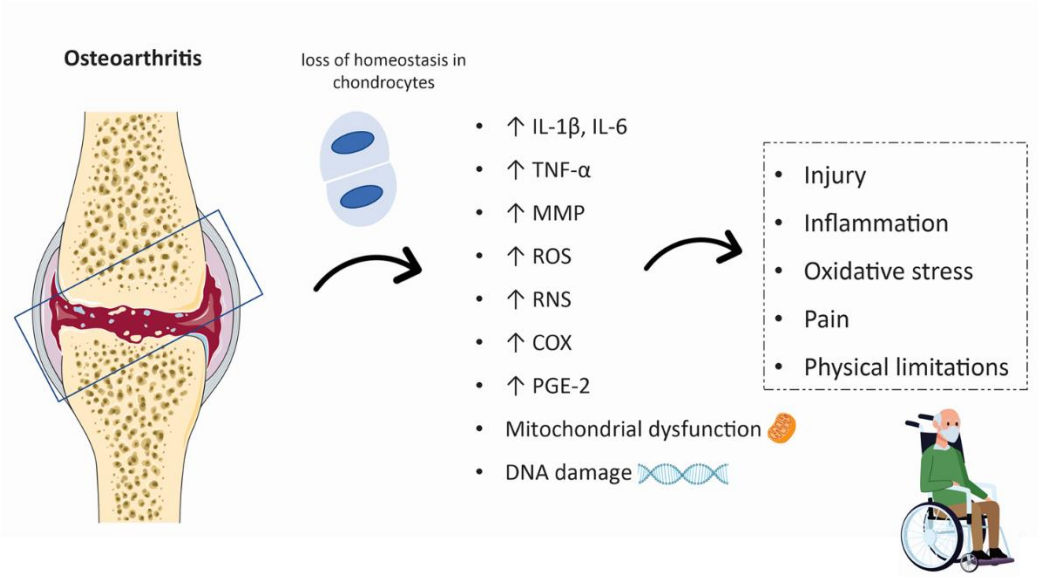


**Figure 4.** Osteoarthritis is associated with the up-regulation in the expression of pro-inflammatory biomarkers leading to injury, pain and physical limitation. COX: cyclooxygenase-2; IL: Interleukin; MMP: metalloproteinase; PGE-2: Prostaglandin E-2; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; TNF-α: Tumor Necrosis Factor-alpha.

OA process can start due to impairment in cartilage healing, aging, loss of cartilage function, and environmental and genetic factors. Typically, it is observed an accelerated cartilage degradation is enforced by an augment of matrix metalloproteinases (MMPs) and metalloproteinase thrombospondin motifs (ADAMTS) (in homeostasis, there is a balance of components of extracellular matrix (ECM) and cartilage degrading enzymes). Alarmins are also increased in OA. These molecules represent the Damage-associated Molecular Patterns (DAMPs) produced as standard cellular components from degraded ECM, which bind to other cells' membranes or intracellular receptors, triggering the inflammatory responses. DAMPs can attach to the Toll-like receptor family, complementing the inflammatory activation and contributing to OA pathogenesis. Moreover, ECM neo-synthesis is reduced in chondrocytes. Furthermore, the characteristic inflammatory process in the joint https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7887204/ - cit0021results in an imbalance release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which have an essential role in the progression of OA, besides the presence of IL-8 and IL-18. The release of cytokines is observed in synovial fibroblasts, macrophages, and chondrocytes. Chondrocytes can undergo apoptosis due to extrinsic factors or mitochondria-associated signaling pathways related to oxidative stress and lysosomal dysfunction. Other inflammatory markers such as cyclooxygenase -2, released by synovial monocytes, and prostaglandins-2 are also involved in the pathophysiology of OA [9,46-48].

The inflammatory stimulus is also related to the release of ADAMTS4 and ADAMTS5 that are aggrecanases and slip aggrecan. After aggrecans degradation, the MMP-3 plays a role in the synergism of proteoglycans degradation. MMPs are related primarily to the degradation of type II collagen and play an essential role in cartilage destruction. MMP-1, MMP-3, MMP-9, and MMP-13 are closely linked to this process, and the MMP-13 is not found in healthy cartilage. The inflammatory scenario and the presence of IL-1β and TNF-α also stimulate the release of MMP. The synoviocytes can also synthesize inflammatory cytokines biomarkers, which amplify the inflammation and cartilaginous destruction [2,49-51].

Mechanical load is a critical risk factor for the development of OA. This risk comes from an excessive mechanical strain over a normal joint due to obesity or occupational risk. It comes from a joint that has waisted its mechano-protective mechanisms. Mechano-protection is based on a stable joint, healthy thick cartilage, and strong muscle that support the joint and intact gait reflexes. Imbalance in these variables is associated with a pro-inflammatory environment named mechanoflammation. It involves the stimulation of the TGF-β-activated kinase 1 (TAK1), which is closely related to the up-regulation of mitogen-activated protein kinases such as p38 and c-Jun N-terminal kinase, and NFκB signaling. TNF-α, and IL-1β also stimulate TAK1 and Toll-Like Receptor (TLR) ligation. TAK1 stimulation leads to relevant pathways associated with the control of aggrecan degradation. Besides, it also stimulated nerve growth factor stimulation, a key mediator of pain in OA [52-54].

The NFκB signaling is related to the pro-inflammatory environment since it releases several cytokines. The stimulation by TNF-α and IL-1β leads to the activation of I Kappa Beta Kinase (IKK), resulting in the phosphorylation of IKB-α. Their degradation products act in the nucleus leading to the activation of numerous genes responsible for producing multiple inflammatory and pro-apoptotic factors [8,55,56].

Parallel to the destruction of cartilage for the reasons mentioned above, a disrupted bone resorption process is observed, and osteoclastogenesis occurs. The receptor activator NFκLigand (RANKL) is released by osteoblast and shows an affinity for RANK leading to phosphorylation pathways resulting in the activation of NFκB. The osteoprotegerin also can bind to RANK, competing with RANKL and leading to apoptosis of mature osteoclasts. [57-59].

Besides inflammation and mechanical load, oxidative stress also has a pivotal role in the degradation of joint tissues, including articular cartilage, synovial membrane, subchondral bone, and meniscus, essential to the maintenance of the functionality of joints. Oxidative stress is characterized mainly by reactive oxygen species, such as superoxide anion radicals, nitric oxide, and peroxynitrite. The repetitive vicious cycle of inflammation and disrupted anabolic-catabolic switch lead to overproduction of reactive species in cartilage, misbalancing the intracellular redox status crucial to regulating mitochondria function chondrocyte hypertrophy, oxidative damages to proteins, lipids, and DNA). For these reasons, oxidative stress results in modifications in the proteins of the cartilaginous matrix found in the endoplasmic reticulum and Golgi compartment of chondrocytes, reducing their synthesis. Moreover,

the excessive free radicals production orchestrates the degradation of the extracellular matrix *via* hydrolysis of matrix components and stimulation of the expression of MMPs that leads to hypertrophic cartilage matrix [60-63].

## 6. OSTEOARTHRITIS, *CURCUMA LONGA*, AND CURCUMINOIDS

Several dietary supplements have been evaluated for OA treatment, but undoubtedly curcumin is the most relevant. The benefits of OA are due to the anti-inflammatory actions of curcumin resulting from the inhibition of inflammatory signals such as leukotrienes, prostaglandins, and COX-2. Moreover, curcumin can suppress the release of TNF-α, IL-1, IL-6, and nitric oxide synthase (Figure 5). Besides that, some authors postulate that special attention should be paid to *Curcuma longa* since it possess other bioactive compounds such as phenolic compounds (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), essential oils (such as ar-curcumene, curcumol, cineole, linalool, caryophyllenezingiberen, turmerone, and α-terpinene), and other components such as campesterol, β-sitosterol, fatty acids, cholesterol, and several elements such as magnesium, potassium, calcium, sodium, iron, zinc). Due to the presence of this plethora of compounds that may act in synergism, *Curcuma longa* can exhibit multi-target and multi-signal pathways in the therapeutic approach to pain and inflammation that are characteristic of OA [64-68].

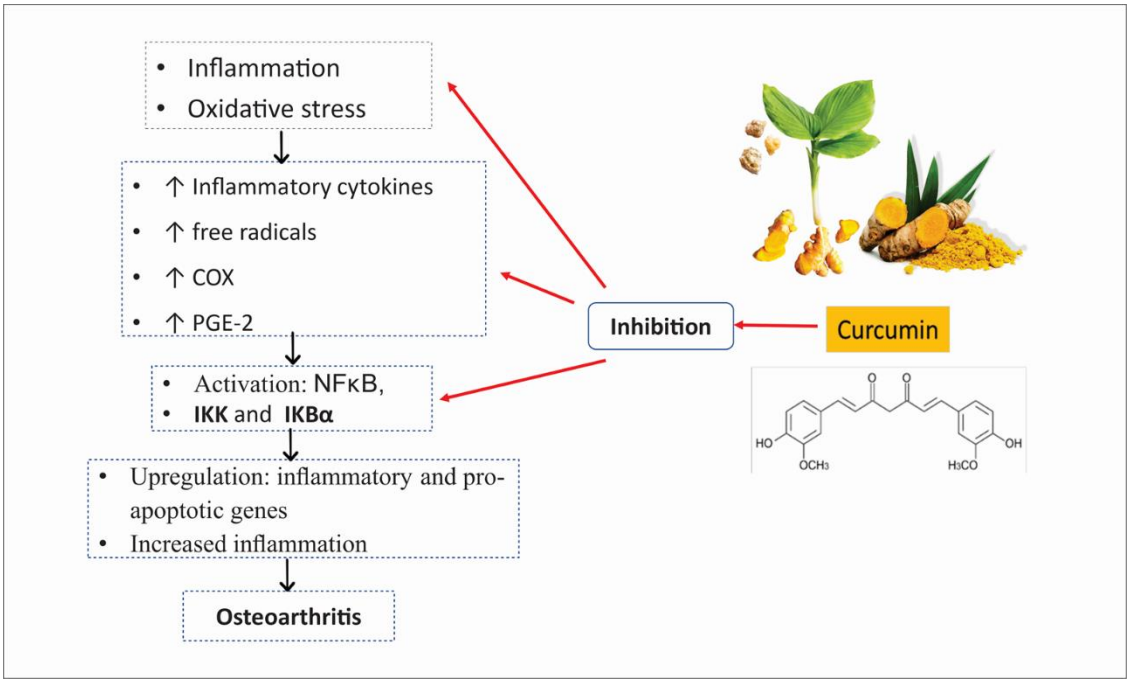


**Figure 5.** Curcumin can inhibit inflammation and oxidative stress due to the downregulation in the expression of pro-inflammatory cytokines, COX-2, PGE-2 and decrease of the production of free radicals. COX: cyclooxygenase-2; IKBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; IKK: I kappa beta Kinase; IL: Interleukin; NFκβ: Nuclear Factor kappa beta; PGE-2: Prostaglandin E-2.

Ross et al [69] performed a Randomized, double-blind, controlled multicenter clinical trial with 367 patients over 50 years possessing OA (rating of knee pain ≥ 5 by the American Rheumatism Association). The subjects received 1.2g daily of ibuprofen or 1.5g daily of curcumin extract (containing 75%-85% curcuminoid; 250 mg of curcuminoids/capsule). After one month, patients presented improvement in WOMAC scores in both groups at weeks 0, 2, and 4 showing that curcumin extract can play a role similar to ibuprofen.

In India, SINGHAL et al. [64], in a Randomized, non-inferiority, controlled clinical study with 144 patients with knee OA (37 men and 107 women and age range of 41-64years), evaluated the effects of BCM-95® (bioavailable turmeric extract / 1000mg /day) or paracetamol for 6 weeks and found that the treated group showed significant improvements in WOMAC total score (pain, stiffness, and function scores), as well as TNF-α and C reactive when comparing to paracetamol group. This RCT was not included in our review since it did not meet the inclusion criteria (not controlled by placebo).

Another randomized trial [70] investigated the effects of BCM-95® with diclofenac or

diclofenac alone for 28 days in patients with OA. It showed that both treatments resulted in improvement in KOOS subscales (pain and quality of life) when compared to diclofenac. Fewer patients needed rescue analgesics in the curcuminoid plus diclofenac group compared to the diclofenac group. The side effects were significantly less in the first group compared to the diclofenac group.

Several other RCTs have been performed to investigate the effects of *Curcuma longa* or curcuminoids in the therapeutic approach of OA, as we show in Table 1. The evaluation of the included studies shows heterogeneity in some aspects, such as the time of the treatment (the follow-up varied from three days to four months), formulations, and the doses (from 180mg to 1500mg/day of curcumin). Regarding administration, all the included RCTs used *Curcuma longa* or curcumin orally.

Concerning the trials included in Table 1, the possible risk of bias is shown in Table 2. PINSORNSAK et al [18] performed the first trial regarding the use of curcumin on OA. This interesting study investigated the effects of curcumin as an adjuvant treatment of diclofenac in primary OA. The authors evaluated KOOS in 5 different categories (pain, symptom, function in daily living, role in sport and recreation, and knee associated quality of life) and found that curcumin associated with diclofenac presented a tendency to improve function in daily living and pain (although without significance). In conclusion, the authors found that the association of curcumin and diclofenac is better than diclofenac alone in the therapeutic approach of OA.

The study of Madhu et al [19] included many more women than men (as observed in almost all the included RCTs). This interesting study showed that the formulation NR-INF02 could bring benefits since it was observed a significant reduction in the VAS, WOMAC, and CGIC compared to placebo, even in a short time (21 and 42 days). Moreover, patients could reduce the rescue medications along with the trial. In another RCT, the authors evaluated the effects of curcuminoids in patients with knee OA and showed improvements in VAS, Lequesne's pain functional index (LPFI), and WOMAC compared with placebo. Nevertheless, this study included a small sample of patients with mild to moderate OA. Moreover, the authors included patients ≤ 80 years, which leads to the inclusion of patients with a large age range [71]. The study of Nakagawa et al [22] evaluated the effects of Theracurcumin in knee OA (Kellegren–Lawrence grade II or III) and found that this compound can reduce pain VAS scores except in participants with initial scores of 0.15 or less. However, this study also included a small sample. Rahiminia et al [23] evaluated the effects of pure curcumin and placebo in patients with mild to moderate OA and found benefits in treating OA symptoms. However, this study also included a small sample.

Using a formulation containing Curcumin BCM95® in patients included in the trial performed by Sterzi et al [24] showed improvements in pain during daily life activities and reduced LPFI. However, the sample size is a limitation of this study. The study performed by Srivastava et al [25] showed improvements in OA scores and oxidative status in patients with OA that used *Curcuma longa* extract. This study does not seem to have any bias since the number of patients, age, allocation, and follow-up are adequate.

Panahi et al [20] investigated the effects of curcuminoids on the systemic oxidative stress in patients with knee OA and suggest that the antioxidant actions observed in these patients are related to the reported relief of OA symptoms. However, as shown in Table 2, many biases are associated with this trial. Moreover, the authors included a small sample of patients ≤ 80 years. Oxidative stress measured by antioxidant enzymes and malonaldehyde production is susceptible to numerous physical exercise and diet factors, which can be very different in patients of very different ages.

Haroyan et al [26] investigated the effects of two formulations (CuraMed® that possess only curcuminoids and Curamin® that possess curcuminoids and boswellic acid). WOMAC and physical performance tests showed that both formulations are superior to placebo but still superior in the Curamin® group. This study was performed with a larger sample compared to the other RCT reducing the risk of bias in interpreting the results. The RCT performed by Panda et al [27] showed the effects of Curene® (a formulation of *Curcuma longa* extract containing naturally derived curcuminoids) in patients with uni or bilateral OA and found that this formulation can significantly reduce stiffness, and pain, and can improve physical functioning. The short sample and the heterogenicity in the included patients' age are the main biases found in this RCT.

Gupte et al [28] investigated the use of solid lipid curcumin particles in patients with knee OA and found it is effective in relieving symptoms. However, this pilot study shows many biases, such as the absence of blind randomization, small sample and missing sample calculation. Henrotin et al [29] studied

the effects of bio-optimized *Curcuma longa* extract in two different doses in patients with knee OA and found that both doses effectively reduce PGADA and inflammatory biomarkers of AO, showing significant reduction of pain reported by patients. The main biases of this study are the small sample size and the inclusion of patients that were non-responders to the standard drugs used to treat OA; thus, they are not sensitive to anti-inflammatory treatments.

Wang et al [31] showed that *Curcuma longa* extracts CL is better than placebo for treating knee pain in OA patients. However, the extract did not modify cartilage composition or knee effusion–synovitis. The main bias of this trial is the small sample and the short duration which may be related to the non-detection of changes in the cartilage.

Calderón et al [30] performed an exciting trial evaluating the acute effects of *Curcuma longa* extracts and insoluble curcuminoids or placebo in participants with knee joint pain. They found that after three days and one week, there was reduced pain if walking on a flat surface, sitting, going up, or downstairs in both groups, but only the treated group showed a reduction in pain during the night, in bed, and an upright posture standing position. Moreover, the group treated with the formulation showed decreased C-reactive protein levels, indicating analgesic actions. This was the first RCT investigating the acute effect of *Curcuma longa* formulation.

The interpretation of our results shows that the use of *Curcuma longa* extracts or formulations prepared with this plant or its bioactive compounds can effectively relief OA symptoms even in short-term studies, as shown by the RCT performed by Calderón-Dias et al [30]. These findings are not in accordance with those from Zeng et al [66] that suggested that the use of *Curcuma longa* extracts or curcumin must last at least three months to achieve therapeutic effects. Moreover, our results show that the therapeutic approach with *Curcuma longa* extracts or formulations with its bioactive constituents can produce effects equivalent to standard drugs considered to the therapeutic approach of OA, however, with much less critical side effects.

## 7. BIOAVAILABILITY AND ADVERSE EFFECTS OF *CURCUMA LONGA*

*Curcuma longa* has been used orally for numerous conditions, but curcumin suffers poor absorption and fast metabolism. Due to these reasons, many researchers have used the combination with other substances such as piperine. This association leads to the increased concentration of curcumin in the blood, the elimination is prolonged, the clearance rate is reduced, and the bioavailability is improved [72-74].

*Curcuma longa* is generally considered well tolerated, even in high doses. However, gastrointestinal symptoms can be observed, such as bloating, nausea, and diarrhea. Allergic reactions have also been reported [75,76].

**Table 1. Randomized Clinical Trials showing the effects of curcumin in Osteoarthritis.**

| Reference | Type of the study and local | Intervention | Outcomes | Adverse events |
|---|---|---|---|---|
| Pinsornsak et al. [18] | Double-blind prospective randomized control trial with 88 patients with OA; 15 men and 73 women (≥ 45 y). Thailand | Patients (n=44) used diclofenac (75 mg/d) with placebo and 44 used diclofenac (75 mg/d) with curcumin (1g/d)/3m. VAS for pain and KOOS were evaluated every month for 3 m. | All patients had improvement in pain (Vas and KOOS scores decreased more in the curcumin group. | NR |
| Madhu et al [19] | Randomized, single-blind, placebo-controlled, comparative study with 120 subjects (37men and 83 women; ≥40y) with knee OA. India | Patients received a placebo (400 mg 2xd) or NR-INF-02 (500 mg 2xd) or GS (750 mg 2xd) alone or a combination of NR-INF-02 and GS/ 42 d. | VAS, WOMAC, and CGIC had significant improvement at each clinical visit compared to placebo. NR-INF-02 promoted a significant reduction with the rescue medication and clinical improvement compared to the placebo | Dyspepsia |

| | | | | |
|---|---|---|---|---|
| Panahi et al [21] | Randomized double-blind placebo-controlled trial; 53 subjects; 80 y, 9 men and 44 women. India | Patients received curcuminoids (1.5g/d in 3 divided doses) or placebo /6 w. WOMAC, VAS, and LPFI scores were evaluated/6w. | The use of curcuminoids significantly reduced WOMAC, VAS, and LPFI compared to placebo. In the WOMAC subscales, it was observed significant improvements in physical function and pain. It was not observed significant differences in VAS, WOMAC, and LPFI between the two groups at baseline. | Mild gastrointestinal symptoms. |
| Nakagawa et al [22] | Randomized, double-blind, placebo-controlled prospective study; 41 subjects with knee OA (Kellgren–Lawrence grade II or III and), ≥ 40 y, 9 men and 32 women. Japan | Patients received a placebo or Theracurmin (180 mg/d)/8w. The symptoms were evaluated at 0, 2, 4, 6, and 2m. | After 8 w, VAS scores significantly decreased in the Theracurmin group. Theracurmin also reduced the celecoxib dependence (more than the placebo group). | No major side effects were observed. |
| Rahimnia et al [23] | Randomized double-blind placebo-control parallel-group clinical trial; 40 patients with mild-to-moderate degree knee OA. Iran | Subjects received pure curcuminoids (1.5g/d; n=19) or placebo (n=21) /6w (curcuminoids were associated with piperine (15 mg/day). | hs-CRP, IL-4, and IL-6 were significantly reduced in both groups | NR |
| Sterzi et al [24] | Multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial; 53 subjects ≥ 50y, 17 men, 33 women. Italy | Participants (n=26) received CartiJoint Forte (chondroitin (400mg), glucosamine hydrochloride (500mg) / 2 tablets, and bio-curcumin BCM-95 (50mg)/d/2m, or placebo. All patients performed 20 sessions of physical therapy along the trial. | No significant difference was seen in VAS between the groups. There were reductions on the Lequesne Index at 8 and 12w compared to 0w, along with the treated group. No significant modifications were observed in inflammation biomarkers and in the knee ROM. | NR |
| Srivastava et al [25] | Randomized, double-blind, placebo-controlled trial; 160 subjects ≥ 50 y, 57 men and 103 women, with knee OA. India | Patients received CL extract (500 mg) or placebo plus the standard treatment (diclofenac 50 mg/day) / 4m. | Significant improvement was observed in EVA and WOMAC in the patients treated with CL. The levels of inflammation and oxidative biomarkers (IL-1β, ROS, and MDA) were significantly improved. | Dyspepsia and nausea. |

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| Panahi et al [20] | Randomized double-blind placebo-controlled parallel-group trial; 40 subjects presenting degenerative primary knee OA with mild to moderate severity and bilateral OA; < 80 years. Iran | Patients received curcuminoids 1.5g/day (n=19); or placebo (n=21)/6w. Curcuminoid capsule contained piperine 5 mg/4m. | SOD, GSH, and MDA in serum were similar between the groups at baseline. The Curcuminoid group presented significant a significant reduction in MDA and elevation in SOD and GSH, attenuating the systemic oxidative stress in the patients and contributing to the relieving OA symptoms. | NR |
| Haroyan et al [26] | Comparative, randomized, double-blind, placebo-controlled study; 201 participants, 40–77y, 187 women and 14 men with degenerative hypertrophic knee OA. Armenia | The subjects received Curamin (350mg curcuminoids + and 150 mg Boswellic acid), CuraMed (333mg curcuminoids) or placebo (500 mg), 3xd /3m. | Curamin® and CuraMed led to improved WOMAC and physical performance tests compared to placebo. Curamed was superior to placebo tests of physical performance. Curcumin and boswellic acid are more effective (due to the synergic effect promoted by the acid). | No adverse effects related to the treatment. |
| Panda et al [27] | Randomized, double-blind, placebo-controlled, parallel-group study; 50 participants, 40-75y presenting unilateral or bilateral knee OA. India | Subjects were divided to receive 500 mg 1xd of Curene® (bioavailable formulation of CL) or placebo/ 3m. | Significant improvements in WOMAC score (also subscale scores) and VAS scores were observed in the treated group compared to the placebo. | Not relevant side effects were reported. |
| Gupte et al [28] | Randomized pilot clinical study; 42 patients ≥65 y, 8 men and 34 women. India | Patients received SLCP (80 mg) 2xd/90d. The control group received Ibuprofen (400 mg) 1xd and placebo (dextrin) in the/ 3m. | Both groups showed significant improvement in WOMAC and VAS scores suggesting comparable effects of SLCP and ibuprofen in alleviating symptoms. | No serious adverse events were reported. |
| Henrotin et al [29] | Double-blind, multicenter randomized placebo-controlled three-arm trial; 141 patients, 113 women and 28 men, 45-80 y with knee OA. Belgium | Participants were allocated in three groups with a ratio of 1:1:1: (a) placebo 2 × 3 caps/d, (b) BCL (46.67mg of CL extract) low dosage (2 × 2 caps/day) plus placebo, and (c) BCL high dosage 2 × 3 caps/day/ 3m. | BCL groups promoted a more significant reduction of PGADA compared to placebo. The global KOOS significantly decreased over time in all groups. | Abdominal discomfort and diarrhea. |

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| Wang et al [31] | Randomized, double-blind, placebo-controlled trial; 70 participant, 31 men, 39 women, > 40 y with knee pain. Tasmania – Australia. | Participants received 1g of CL (extract with 80% wt/wt aqueous-based, with turmerosaccharides + 20% wt/wt curcuminoids) or /3m. | CL led to improvement in VAS (but did not modify effusion–synovitis volume) and WOMAC knee pain. | Adverse events were similar in both groups (allergy and gastrointestinal symptoms). |
| Calderón et al [30] | Randomized, pilot clinical trial, 68 subjects (29 men, 39 women, 18-65y with mild-to-moderate-intensity knee joint pain, scored 6 to10 of 20 points in the WOMAC score pain subscale). Spain | Participants received B-Turmactive (500 mg of turmeric extract + 19.5 mg of curcuminoid complex) or placebo/ 1w. | After 3 d and 1 w, both treatments decreased pain during walking, going up or downstairs, and sitting or lying, but only turmeric decreased pain at night in bed. B-Turmactive also reduced C reactive protein at 1 week, indicating an analgesic effect due to decreased inflammatory biomarkers. | NR |

OA: Osteoarthritis; VAS: Visual Analog Scale; KOOS: Knee injury and Osteoarthritis Outcome Score; NR-INF-02: Bioactive Turmerosaccharides from *Curcuma longa* Extract; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; AE: Adverse events; LPFI: Lequesne's pain functional index; IL-4: interleukins 4; IL-6: interleukins 6; TNF- α: tumor necrosis factor-α; hs- CRP: high-sensitivity C-reactive protein; CL: *Curcuma* longa; MDA: malondialdehyde; SOD: superoxide dismutase; GSH: glutathione; MDA: malondialdehyde; KOOS: Knee Injury and Osteoarthritis Outcome Score; SLCP: solid lipid curcumin particles; BCL: Bio-optimized *Curcuma* longa extracts; PGADA: Patient Global Assessment of Disease Activity; AE: adverse events; y: year; m: month; w: week.

Table 2. Descriptive table of the biases of the included randomized clinical trials.

| Study | Question focus | Appropriate randomization | Allocation blinding | Double-blind | Losses (<20%) | Prognostics or demographic Characteristics | Outcomes | Intention to treat analysis | Sample calculation |
|---|---|---|---|---|---|---|---|---|---|
| Pinsornsak et al. [18] | Yes | Yes | Yes | Yes | ? | Yes | Yes | ? | ? |
| Madhu et al [19] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Panahi et al [21] | Yes | Yes | ? | Yes | No | Yes | Yes | NR | No |
| Nakagawa et al [22] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR | No |
| Rahimnia et al [23] | Yes | Yes | Yes | Yes | No | Yes | Yes | NR | No |
| Sterzi et al [24] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Srivastava et al[25] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Panahi et al [20] | Yes | Yes | ? | Yes | No | No | Yes | NR | No |
| Haroyan et al [26] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Panda et al [27] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Gupte et al [28] | Yes | No | No | No | Yes | Yes | Yes | No | No |
| Henrotin et al [29] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Wang et al [31] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Calderón et al [30] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

NR: Not reported.

## 8. CONCLUSION

The use of *Curcuma longa* extracts or curcuminoids can benefit patients with OA. Nevertheless, the available clinical trials show relevant heterogeneity since the treatment time is different and the administered doses and the type of formulation used. Thus, the standardization of clinical trials can guide researchers and physicians as to the dosages and formulations that are most effective in addressing this condition, which is very prevalent in the world's populations.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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